April 28, 2017

Improving the Quality of Care: Overutilization of Proton Pump Inhibitors

Learning Objectives:

- Review the appropriate indications for short-term and long-term use of proton pump inhibitors (PPIs)
- Describe potential adverse effects associated with use of PPIs
- Summarize best practices for responsible prescribing of PPIs

Key Points:

- PPIs are one of the most commonly prescribed medications in the United States, but an estimated 25% to 70% of these prescriptions have no appropriate indication for PPIs.
- PPI use may be associated with an increased risk of both acute and chronic kidney disease, hypomagnesemia, *Clostridium difficile* infection, osteoporotic fractures, and dementia.
- For patients with gastroesophageal reflux disease (GERD) without contraindications to PPIs, an eight-week course of PPIs is the first-line pharmacotherapy of choice for symptom relief.
- Within the Medi-Cal fee-for-service population, 77% of beneficiaries with a paid claim for a PPI between November 1, 2015, and October 31, 2016, had no indication for potentially appropriate use of PPI therapy and 85% of long-term users showed no attempt at tapering off PPIs during a one-year period.

Background

PPIs, typically used to reduce gastric acid, are one of the most commonly prescribed medications in the United States.[1-3] However, an estimated 25% to 70% of these prescriptions have no appropriate indication for PPIs (see Table 1).[2-5] Treatment with PPIs often continues well beyond recommended guidelines, and there is increasing data showing that PPIs are associated with a number of adverse effects.[1-9] Current evidence now suggests PPI use may be associated with an increased risk of both acute and chronic kidney disease, hypomagnesemia, *Clostridium difficile* infection, osteoporotic fractures, and dementia.[1-9] A recent comparative study found an increased risk of chronic kidney disease specific to long-term use of PPI medications, while finding no increased risk with long-term use of H_2-receptor antagonists, which are prescribed for the same indications as PPIs.[7]

Table 1. Appropriate Indications for Use of Proton Pump Inhibitor Therapy[3,4,10]

Duration of Therapy	Indication
Short-term (approximately eight weeks)	GERD
	Gastric and duodenal ulcers
	Helicobacter pylori infection
	Stress ulcer prophylaxis
Long-term (may continue for longer than a year)	Refractory GERD
	Erosive esophagitis
	Zollinger-Ellison Syndrome
	NSAID-induced ulcers
	Chronic anticoagulation after a gastrointestinal (GI) bleed
	Barrett's esophagus

PPIs are a highly effective class of drugs and will continue to be the primary symptomatic treatment for patients with upper GI conditions.[1] However, the strong evidence supporting PPI efficacy and a relatively favorable safety profile may have contributed to overutilization of PPIs.[2-5] Use of PPIs should be indication-specific, evidenced-based, and follow established clinical guidelines.[4,10] All pharmacotherapy options for treating GERD that appear on the Medi-Cal List of Contract Drugs are included in Table 2.

Table 2. Pharmacotherapy for Treating GERD on the Medi-Cal List of Contract Drugs

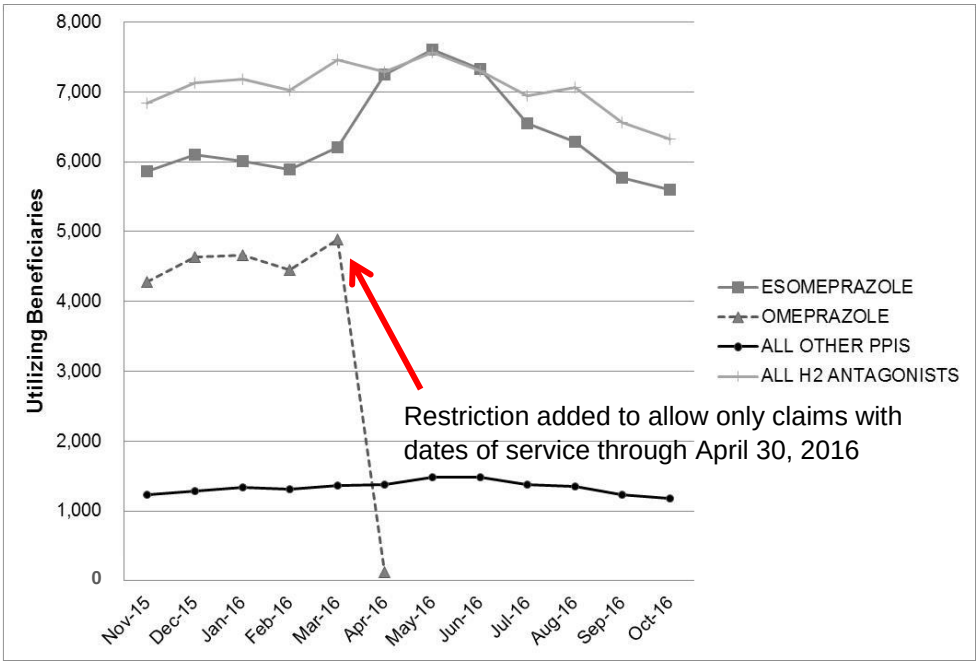
Drug Therapeutic Category and Recommendations	**Drug***
Proton Pump Inhibitors: • An 8-week course of PPIs is the first-line pharmacotherapy of choice for symptom relief and healing of erosive esophagitis • No major differences in efficacy between the different PPIs	Dexlansoprazole • Capsules: 30 mg, 60 mg
	Esomeprazole • Capsules: 20 mg, 40 mg
H_2-Receptor Antagonists: • Prescribe a bedtime dose, as needed, in patients with nighttime symptoms and/or objective evidence on pH monitoring of overnight esophageal acid reflux despite optimal PPI use • First-line replacement therapy for PPIs in patients with low magnesium levels, the elderly, and patients at high risk for *C. dificile* infection, bone fractures, or kidney disease • Can be used after PPI discontinuation as needed for breakthrough symptoms	Cimetidine • Tablets: 300 mg, 400 mg, 800 mg • Oral solution: 300 mg/5 ml
	Famotidine • Tablets: 20 mg, 40 mg • Oral suspension: 40 mg/5 ml
	Ranitidine • Tablets: 150 mg, 300 mg
Intestinal Motility Stimulants: • Consider adding to medication regimen for those patients not responding to PPI therapy	Metoclopramide • Tablets: 5 mg, 10 mg • Oral solution: 5 mg/5 ml
Antacids: • Do not usually provide sufficient acid suppression for patients with GERD as monotherapy • Prescribe as needed in patients with nighttime symptoms • Only relieve symptoms in the short term rather than preventing them • Can be used after PPI discontinuation as needed for breakthrough symptoms	Aluminum hydroxide • Oral suspension: 320 mg/5 ml
	Calcium carbonate • Tablets: 260 mg
	Alginic acid/aluminum/magnesium/sodium bicarbonate • Chewable tablets: 14.2 – 80 mg, 20 – 80 mg
	Aluminum hydroxide/magnesium hydroxide/simethicone • Chewable tablets: 200-200-25 • Oral suspension: 200-200-25

* Some medications may have additional restrictions on manufacturer codes. For current information, use the online Medi-Cal Formulary search tool available on the Formulary File Web page of the Department of Health Care Services (DHCS) website.

Proton Pump Inhibitor Use in the Medi-Cal Fee-for-Service Population

As shown in Figure 1, when a date of service restriction was added to over-the-counter (OTC) omeprazole in the Medi-Cal fee-for-service program in April 2016, the total number of utilizing beneficiaries went from approximately 5,000 to close to zero. There was a slight increase in utilizing beneficiaries with a paid claim for other PPIs and H_2-receptor antagonists for the next two months, but after June 2016, utilization for these drugs went back to previous levels.

Figure 1. Utilization of Proton Pump Inhibitors and H_2-receptor Antagonists (with dates of service between November 1, 2015, and October 31, 2016)



In order to further evaluate the use of PPIs in the Medi-Cal fee-for-service population, a retrospective cohort study was conducted using pharmacy and medical claims data. The initial study population included all Medi-Cal fee-for-service beneficiaries with at least one paid claim for a PPI between November 1, 2015, and October 31, 2016 (the measurement year) who were continuously eligible in the Medi-Cal fee-for-service program during the measurement year.

In order to determine the appropriateness of prescribing PPIs, all available medical claims data were reviewed during both the measurement year and the year prior to the measurement year. Any beneficiary with one of the following primary or secondary ICD-10-CM diagnosis codes within that two-year timeframe was coded as a potentially appropriate use of a PPI:

- *H. pylori* infection (B96.81)
- Zollinger-Ellison Syndrome (E16.4)
- GERD (K21.0 and K21.9)
- Esophagitis (K20.0 – K20.9)
- Barrett's esophagus (K22.7)
- Gastric, duodenal, and peptic ulcers (K25.0 – K25.9, K26.0 – K26.9, K27.0 – K27.9)
- GI hemorrhage (K92.2)

Diagnosis codes were also reviewed for any beneficiaries with a paid claim for PPI therapy that had a comorbid primary or secondary diagnosis of acute kidney injury and/or chronic kidney disease. Concomitant use of other GERD medications, including antacids, H_2-receptor antagonists, and metoclopramide, were also reviewed. Monitoring rates for serum creatinine and magnesium were also calculated for the study population during the measurement year. Demographic characteristics, including gender, age, race/ethnicity, and geographic region of residence, were reviewed for all beneficiaries in the study population.

Results

A total of 23,921 continuously-eligible Medi-Cal fee-for-service beneficiaries had at least one paid claim for a PPI between November 1, 2015, and October 31, 2016. Within the study population, most beneficiaries had three or fewer paid claims for PPIs (68%) during the measurement year and/or for PPI treatment duration of 90 days or less (61%). However, there were 2,995 beneficiaries (13%) categorized as long-term users of PPI therapy, with at least 300 treatment days of PPI therapy during the measurement year.

The majority (n = 18,455; 77%) of PPI use during the measurement year did not appear to be related to treatment for an appropriate indication for either short-term or long-term PPI therapy. Potentially inappropriate use of PPI therapy was approximately the same among the long-term users, with 75% of long-term users not having an appropriate indication for PPI therapy during the measurement year or the year prior to the measurement year. Long-term users of PPI therapy were more likely to have serum creatinine monitoring (81% v. 69%) and magnesium monitoring (26% v. 19%) during the measurement year. A total of 50 beneficiaries (2%) categorized as long-term users had a comorbid diagnosis of kidney disease during the measurement year. Among long-term users, only 450 beneficiaries (15%) had a break from PPI therapy during the measurement year of at least 30 days.

Concomitant use of other medications within the study population is shown in Table 3, stratified by the presence or absence of a potentially appropriate indication for PPI therapy.

Table 3. Concomitant Use of Selected Medications (During the Measurement Year)

	Potentially Appropriate PPI Use (n = 5,466)	**Potentially Inappropriate PPI Use (n = 18,455)**
	n (%)	**n (%)**
Concomitant use of additional GERD medications:		
• H_2-receptor antagonists	1,140 (21%)	2,215 (12%)
• Metoclopramide	522 (10%)	1,012 (6%)
• Antacids	349 (6%)	701 (4%)

Beneficiaries with potentially appropriate indications for use of PPI therapy were more likely to have concomitant use of H_2-receptor antagonists, metoclopramide, and antacids. Of note, these data only include paid pharmacy claims and do not include over-the-counter medications in which beneficiaries did not have a prescription through the Medi-Cal fee-for-service program.

The demographic characteristics of the study population are shown in Table 4, also stratified by the presence or absence of a potentially appropriate indication for PPI therapy.

Table 4. Demographic Characteristics of the Medi-Cal Fee-for-Service Study Population

	Indication for Potentially Appropriate PPI Use n (%)	No Indication for Potentially Appropriate PPI Use n (%)
Overall population (n = 23,921)	**5,466 (23%)**	**18,455 (77%)**
Gender		
• Male (n = 8,828)	2,209 (25%)	6,619 (75%)
• Female (n = 15,093)	3,257 (22%)	11,836 (78%)
Age		
• 39 years of age and younger (n = 8,613)	2,302 (27%)	6,311 (73%)
• 40 years of age and older (n = 15,308)	3,164 (21%)	12,144 (79%)
Race/Ethnicity		
• White/Caucasian, non-Hispanic (n = 5,520)	1,352 (24%)	4,168 (76%)
• All other races/ethnicities (n = 18,401)	4,114 (22%)	14,287 (78%)
California Region of Residence		
• Los Angeles County (n = 9,419)	2,036 (22%)	7,383 (78%)
• All other regions/counties (n = 14,502)	3,430 (24%)	11,072 (76%)

The demographic characteristics of beneficiaries with a paid claim for potentially appropriate PPI use were similar to those of beneficiaries without an indication for potentially appropriate use. However, those beneficiaries 39 years of age and younger were more likely to have an indication for a potentially appropriate use of PPI therapy than among those beneficiaries 40 years of age and older. Of note, out of the 25 infants (less than one year of age) with a paid claim for a PPI during the measurement year, a total of 20 (80%) had no indication for a potentially appropriate use of PPIs.

Conclusion/Discussion

The overall benefits of therapy and improvement in quality of life significantly outweigh potential risks in most patients.[1] However, patients who lack a clear indication for appropriate use of PPI therapy should be reevaluated at each prescription refill in order to determine if PPI therapy can be safely discontinued or if an alternative treatment regimen may be needed. By supervised tapering of PPIs, a substantial number of patients treated with PPIs without a clear indication can discontinue PPIs or lower the dose of PPI therapy, reducing their long-term risk of adverse events.

Clinical Recommendations

- Encourage the following non-pharmacologic/lifestyle management as first-line treatments for GERD symptoms:
  - Elevating the head of the bed six inches
  - Avoiding meals two to three hours before bedtime
  - Weight loss, if appropriate
  - Smoking cessation
  - Psychological stress reduction, if necessary
  - Ensure adequate sleep
- Periodically consider tapering PPIs in patients receiving prolonged therapy.
- Prescribe PPIs only for clearly documented indications and for the shortest duration possible.
- Exercise caution in the elderly and in patients with other risk factors for *C. difficile* infection or bone fractures.
- Recommend reevaluating PPI indications at transitions of care as an opportunity to eliminate unnecessary therapy.
- Recommend antacids or H_2-receptor antagonists as needed for breakthrough symptoms after PPI discontinuation.
- For patients requiring long-term PPI therapy or high doses of PPIs, follow recommended monitoring guidelines for serum creatinine and magnesium levels:
  - Be familiar with concomitant medications that can lower magnesium levels (for example, thiazides, loop diuretics).
  - Closely monitor patients with concomitant use of digoxin, as digoxin toxicity can occur with low magnesium levels.
  - Recommend OTC magnesium supplements to treat low magnesium levels.
  - Consider replacing PPI with an H_2-receptor antagonist if magnesium levels do not improve with supplementation.

References:

1. Schoenfeld AJ and Grady D. Adverse effects associated with proton pump inhibitors. *JAMA Intern Med*. 2016 Feb;176(2):172-4.
2. Forgacs I and Loganayagam A. Overprescribing proton pump inhibitors. *BMJ*. 2008;336(7634):2-3. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2174763/pdf/bmj-336-7634-edit-00002.pdf. Accessed: April 9, 2017.
3. Katz MH. Failing the acid test: benefits of proton pump inhibitors may not justify the risks for many users. *Arch Intern Med*. 2010;170:747-8.
4. Heidelbaugh JJ, Kim AH, Chang R, Walker PC. Overutilization of proton-pump inhibitors: what the clinician needs to know. *Therap Adv Gastroenterol*. 2012;5:219-32.
5. Heidelbaugh JJ, Goldberg KL, Inadomi JM. Magnitude and economic effect of overuse of antisecretory therapy in the ambulatory care setting. *Am J Manag Care*. 2010;16:e228-34.

6. Wilhelm SM, Rjater RG, Kale-Pradhan PB. Perils and pitfalls of long-term effects of proton pump inhibitors. *Expert Rev Clin Pharmacol*. 2013;6(4):443-451.
7. Lazarus B, Chen Y, Wilson FP, et al. Proton pump inhibitor use and the risk of chronic kidney disease. *JAMA Intern Med*. 2016;176(2):238-246.
8. Gomm W, von Holt K, Thomé F, et al. Association of proton pump inhibitors with risk of dementia: a pharmacoepidemiological claims data analysis. *JAMA Neurol*. 2016 Apr;73(4):410-6.
9. FDA. FDA drug safety communication: low magnesium levels can be associated with long-term use of proton pump inhibitor drugs (PPIs). March 2, 2011. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm245011.htm. Accessed: April 9, 2017.
10. Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. *Am J Gastroenterol*. 2013;108:308-28. Available at: http://gi.org/wp-content/uploads/2013/10/ACG_Guideline_GERD_March_2013_plus_corrigendum.pdf. Accessed: April 3, 2017.